The Old Drug Ketamine Keeps on Surprising Us

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In this issue of *Anesthesia & Analgesia*, Linassi et al[1] report interesting findings about the consequences of the administration of a bolus of ketamine on the evolution of the Bispectral Index (BIS), the 95% spectral edge frequency (SEF95) of the electroencephalogram (EEG), and the Surgical Plethysmographic Index (SPI) over time. Ketamine administration occurred in a group of 14 female patients undergoing breast surgery, during a steady-state propofol-remifentanil target-controlled infusion (TCI) and surgical stimulation (AA-D-23-01598R1). The bolus of ketamine was also delivered using TCI running the Domino's model,[2] allowing to obtain estimates of ketamine effect-site concentration over time, and to parallel them with the evolution of the studied parameters. The authors observed an increase in BIS and SEF95 after ketamine administration but noticed a delay of several minutes between the moment of ketamine theoretical peak concentration as defined by the TCI model, and BIS and SEF95 maxima. Contrarily, despite the well-known antinociceptive effect of ketamine, they did not observe any relevant changes in SPI values during the minutes after the ketamine bolus.

These results provide important information about the kinetics of the pharmacodynamic effects of a moderate dose of ketamine when given as a bolus during stable anesthetic and surgical stimulation conditions. Those kinetics should be considered by the clinician when interpreting the value of EEG-derived indexes and the value of autonomic nervous system activity-derived nociception indexes. They raise the question of the pharmacological mechanisms behind and should also be interpreted at the light of the weaknesses of the study itself, which preclude from directly transposing them to any other anesthetic and surgical situation.

LIMITATIONS OF THE CONSIDERED STUDY

Before envisaging the mechanisms potentially explaining Linassi et al observations, let's consider the main limitations of their study, which are adequately commented in their manuscript but should be again stressed out here.

First, according to the study protocol, steady-state anesthesia before ketamine administration was reached after adjusting propofol concentration to obtain a BIS value between 40 and 60, and an SPI value between 20 and 50. These are relatively wide ranges of index values. This may have introduced bias, insofar as the brain activity and related EEG are not the same at a BIS of 40 as compared to a BIS of 60. The same is true regarding the sympathetic/parasympathetic balance at an SPI of 20 or an SPI of 50. Additionally, the same BIS or SPI value can be obtained with very different propofol-remifentanil combinations, and the consequences of ketamine administration on each of the considered index might not be the same when starting from different propofol or remifentanil baseline. However, when looking at the results reported in Table 1 of the paper, it appears that this limitation has probably had little effect on the reported results, because the variance of the concentrations at steady-state is remarkably small.

Second, the sample size of their study is not large. This may have precluded them from evidencing statistically significant effects, notably regarding the evolution of SPI after ketamine administration. When looking at the authors' Figure 4, it seems that SPI tends to decrease shortly after ketamine has reached its theoretical peak concentration, and that the lowest SPI value after ketamine administration is much lower than the baseline SPI value. The authors are right when arguing that an absence of significant change in SPI might be due to an already deep baseline antinociception level and/or to an increase in sympathetic tone by ketamine.[3] It might also be that they missed that effect due to the small sample size.

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Third, the selected population concerned relatively young (approximately 52 to 66 years) female patients in good health (American Society of Anesthesiologists [ASA] physical status I or II), undergoing breast surgery. Transposition of the obtained results to another age group, as we know that EEG power spectrum and complexity changes as we age,[4] to sicker patients, to other types of surgeries eliciting other levels of noxious stimulation intensity, and to males, which are known to be more sensitive to the effects of anesthetic agents,[5] should be made very cautiously.

Fourth, it should be stressed out that Linassi's results are based on estimations of ketamine effect-site concentrations according to the Domino's model,[2] and not on a direct measurement of ketamine concentrations. Other models than the Domino's one have better performance at estimating these concentrations,[6] and the exchange constant (ke0) used in the model to estimate the equilibration kinetics between the central and the effect-site compartments might not be accurate. Pharmacodynamic observations like the ones of Linassi might serve to refine ketamine ke0 determination. Nevertheless, the delay between ketamine administration and changes in the EEG is certainly a reality, and is the consequence of the combined influence of the time needed for equilibration of concentrations between the central and the effect-site compartment, the time needed for BIS and SEF95 calculation and display by the monitoring device, and possibly the time needed for a stabilization of the balance between the excitatory and inhibitory influence of ketamine on brain activity, as discussed below.

Having listed the points of Linassi's study that can be debated, one may now consider the original properties of ketamine explaining its paradoxical effects on the EEG, and the clinical implications all this might have.

THE ORIGINAL PROPERTIES OF KETAMINE AND THEIR CONSEQUENCES ON THE ELECTROENCEPHALOGRAM

Ketamine effects on the central nervous system are dose-dependent and complex. At the brain level, ketamine might influence neuronal activity in opposite directions. On the excitatory side, ketamine can induce an indirect excitation of pyramidal neurons through an antagonism of the N-methyl-D-aspartate (NDMA) glutamate receptors on inhibitory interneurons (hence through an inhibition of an inhibition).[7] Through a similar mechanism (an inhibition of inhibitory γ-amino-butyric-acid (GABA)ergic neurons, which normally inhibit glutamatergic excitatory interneurons that project onto aminergic neurons), it favors the release of dopamine, acetylcholine, and other amines, which are known to boost cortical arousal.[8] On the inhibitory side, it can block neuronal activity through NMDA antagonism or through the blocking of hyperpolarization-activated cation channels.[7] The net result is variable, depending on the administered dose, and depending on whether ketamine is administered alone or in association with other anesthetic agents with, for example, GABAergic properties. This equilibrium can balance between dominant excitation, for example when the increased amine activity wins out,[9] and dominant inhibition. When ketamine is administered alone, the reported brain activity changes include an increased activity in several brain regions (eg, the midcingulate cortex, the dorsal part of the anterior cingulate cortex, the insula bilaterally, the posterior cingulate, the precuneus, the lingual gyrus, the hippocampus, and the thalamus), while other regions are inhibited (eg, the subgenual/subcallosal part of the anterior cingulate cortex, the orbitofrontal cortex and the gyrus rectus),[10] a complexity of brain communication that is close to the one of the waking state,[11] a fronto-parietal alteration in communication,[12] particularly in the α EEG bandwidth[13] and within the default-mode network thought to support internal awareness (or internal thoughts), a preservation of connectivity within the executive control network (thought to be responsible for attention switching and connectedness to the environment), and a preservation of connectivity within lower-order sensory networks.[14] It is not easy, however, to precisely relate those changes to phenomenological observations like responsiveness to stimulation, presence of dreams, … The consequences of those changes on the EEG are also dose-dependent, and include the presence of γ bursts, the presence of a β-γ pattern on the spectrogram, increased frontal θ activity, and the presence of episodic slow delta waves,[15] which results from up and down neuronal states generated through the above-mentioned NMDA and GABA receptors interactions.[16] It seems that this slow wave activity witnesses the loss of consciousness.[15,16] Any change in the EEG activity towards higher frequencies (such as increased β-γ activity) determines an increase in BIS and SEF95. Contrarily, when the inhibitory effect of ketamine predominates or is potentiated by other agents with GABAergic properties, the EEG turns out to lower frequencies like the γ-burst pattern, frontal θ, and slow δ, and this is related to changes in thalamocortical interactions. This may dampen the BIS and SEF95 values.

The antinociceptive effects of ketamine result from central and peripheral effects, including among others a direct inhibition of NMDA receptors at the level of the dorsal horn, the modulation of the release of neuromodulators, interactions with the sympathetic autonomic nervous system, and the promotion of the activity of the descending nociception inhibitory pathways.[7] These effects might not necessarily have

repercussions on indexes that are derived from the activity of some autonomic nervous system target organs, particularly if nociception is already inhibited by high doses of opioids.

CLINICAL IMPLICATIONS AND CONCLUSIONS

Clearly, adding ketamine to a baseline anesthetic regimen alters the ability of anesthesiologists to adequately appreciate the real depth of the hypnotic component of anesthesia, not only because it can provoke paradoxical changes in EEG-derived indexes, as reported on several occasions, but also because the timing of those changes is offset as compared to the moment of ketamine administration. Hence, the clinician should expect changes in the EEG, with some delay from the moment of injection, and should use all available information to interpret these changes. In this respect, simply looking at an EEG-derived index like the BIS is not enough. Currently in routine practice, the only way to detect specific patterns like γ-burst, β-γ activity, increased slow δ, frontal α weaning, and frontal θ is to look at the evolution of the EEG power spectrum over time, on the density spectral array displayed by several commercially available monitors. This is a supplementary reason for equipping our anesthesia stations with EEG monitors that offer such a display. Regarding nociception monitoring, dedicated studies are needed to better understand the complex relationship between the underlying antinociceptive regimen, the addition of ketamine to it at variable doses, and the kinetics of the consequences on the autonomic nervous system-derived indexes of nociception. Even though ketamine has now been used for a very long time in anesthesia, there is still a need to study its properties in depth, to resolve the riddles it continues to hold for us.

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